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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/551,203	06/29/2006	Simon Michael West	051-167-US	4056
718 REED SMITH LLP P.O. BOX 488 PITTSBURGH, PA 15230-0488	7590 09/07/2007		EXAMINER MAEWALL, SNIGDHA	
			ART UNIT 1615	PAPER NUMBER
			MAIL DATE 09/07/2007	DELIVERY MODE PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/551,203

Applicant(s)

WEST ET AL.

Examiner

Snigdha Maewall

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on ____.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-18 and 21-24 is/are pending in the application.
- 4a) Of the above claim(s) ____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) ____ is/are allowed.
- 6) ☒ Claim(s) 1-18 and 21-24 is/are rejected.
- 7) ☐ Claim(s) ____ is/are objected to.
- 8) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. ____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date 06/08/2007.
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. ____.
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: ____.

DETAILED ACTION

Summary

1. Receipt of Applicants Arguments/Remarks, Amended Claims and Information Disclosure Statement filed on 06/08/2007 is acknowledged. Claims 19-20 have been cancelled, claims 2-18 and 22 have been amended and new claims 23-24 have been added in this application. Accordingly, **claims 1-18 and 21-24** are pending in this application and **claims 1-18 and 21-24** will be prosecuted on the merits.

In view of Applicants Arguments, the 35 USC 112 rejections have been withdrawn however; the following rejections of record are maintained.

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1,148

USPQ 459 (1966) that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.

2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

3. Claims 1-3, 6, 8-18 and 21-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kirby et al. U.S. Patent No. 6,444,234 B1 (herein after '234) in view of WO 02/40033 A1 (herein after '033) or vice-versa.

Kirby et al. discloses:

Pharmaceutical compositions for the transdermal administration of a medicament or active agent by topical application of the composition to the skin of humans or animals (abstract).

- '(234) Also teaches a method for formulating safe and effective compositions for topical transdermal applications of an active agent such as morphine (column 5 lines 3-5 and col. 42 example 14). The composition as set forth by ('234) comprises an active agent in a "carrier". Said "carrier" comprises solvent and modifying agents. The solvent modifiers facilitate the dissolution of the active agent and formation of the weak association which enable the complex of active agent-modifier to pass the defensive of the skin with minimal irritation without modification of the chemical structure or stereoscopic configuration of the active agent (column 11, lines 5-10). The solvent modifiers selected do not form permanent or strong covalent bonds with the medicament or active agents; instead they form complexes that facilitate the movement of the complex past the viable skin to its targeted site (column 5 lines 53-56).

Although ('234) discloses the use of solvent modifiers in formulating pharmaceutical compositions for the transdermal administration of a medicament or active agent, ('234) does not explicitly teach using phosphate derivatives of tocopherol or other tocols as claimed in the instant application as solvent modifiers for the same purpose. However, WO 02/40033 A1 ('033) teaches an efficacious therapeutic emulsion formulation for therapeutic administration comprising phosphate derivatives of "electron transfer agents" and an "acceptable carrier" (abstract).

- According to ('033), the use of a phosphorylated electron transfer agent plays therapeutic and efficacious role in dermal penetration (page 3, lines 3-8).
- The "electron transfer agents" as indicated by ('033), refer to the class of chemicals, which may be phosphorylated. Examples of classes of "electron transfer agents" that may be phosphorylated include hydroxyl chromans including alpha, beta and gamma tocopherol, tocols and tocotrienols in enantiomeric and racemic forms; quinols being the reduced form of vitamin K1 and ubiquinone; hydroxyl carotenoids including retinol and ascorbic acid (page 3, lines 26-28 and page 4, lines 1-2). The phosphate derivatives may exist in the form of a free phosphate acid, a salt thereof, a di-phosphate ester thereby including two molecules of electron transfer agents, a mixed ester including two different compounds selected from electron transfer agents, or a phosphatidyl compound (page 4, lines 5-9).

- ('033) further teaches that the phosphate derivatives of "electron transfer agents" can be combined with "acceptable carrier". As defined in ('033), the "acceptable carrier" could be referred to a "carrier" considered by those skilled in the drug, food or cosmetic arts to be non-toxic when used to treat humans, animals or plants in parenteral or enteral formulations. The "carrier" will depend on the route of administration and the ingestible formulations, which include tablets, capsules, powders etc. (see page 4, lines 30-33 and page 5, lines 1-6). ('033) further teaches that phosphate derivative may exist in the form of a phosphatidyl compound wherein the free phosphate oxygen forms a bond with an alkyl group or a complex with a complexing agent selected from amphoteric surfactant, cationic surfactant or aminoacids having nitrogen functional groups or proteins rich in these amino acids (see page 4, lines 8-11 and claim 4).

Since phosphate derivatives of tocopherol has been shown to form complex with aminoacids having **nitrogen functional groups**, it is therefore proven that **nitrogen** is the critical element in forming a complex with tocopherol phosphate. Based on the foregoing, it would have been obvious to one of ordinary skilled in the art at the time of the invention to use the phosphate derivatives of tocopherol ('033) in the compositions of ('234) comprising an alkaloid such as morphine which bears a functional nitrogen, to form a complex. Or alternately to use morphine taught by ('234) in the generic teachings of ('033) which discloses that phosphate derivatives of electron transfer agents such as tocopherol phosphate derivatives posses an unexpected property in exhibiting an efficacious role in dermal penetration of the therapeutically active formulation such as

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topical formulations or formulations such as tablets, powders, chewable tablets, capsules, oral suspensions, children formulations, enteral feeds or nutraceuticals, would have been obvious to one skilled in the art at the time of invention with a reasonable expectation of success since ('033) is directed to transdermal delivery and ('234) shows that morphine can be administered transdermally.

4. Claims 4, 6-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schor et al. (U.S. Patent No. 4,369,172, herein after ('172) in view of WO 02/40033 A1 ('033) or vice versa.

The teachings of Schor et al. and WO 02/40033 A1 ('033) are disclosed above.

With respect to claims 4, 6-7, Schor et al. teaches,

- Schor et al. ('172) discloses an invention which provides a "carrier material" for use in the preparation of orally, buccally or sublingually administered lozenges and tablets that have a regular and prolonged release pattern for systemically absorbable medicament or active ingredient incorporated therein. Said "carrier material" as defined by Schor et al. is hydroxypropylmethylcellulose (column 2, lines 41-48 and title).
- ('172) teaches that the active ingredient can be of the type of medication which acts locally in the mouth or systemically which in the case of latter can be administered orally to transmit the active medicament into the gastrointestinal tract and into the blood fluids and tissues of the body (column 5, lines 42-50).
- ('172) further discloses that active ingredient can be of the type of medication

which acts through the buccal tissues of the mouth to transmit the active ingredient directly into the blood stream.

- ('172) further discloses that morphine can be used as an active ingredient (see column 6, line 53 and column 2, claim 23).

Schor et al. ('172) does not teach using phosphate derivatives of "electron transfer agents". However, ('033), as discussed above, teaches forming complex of tocopherol phosphate derivative with aminoacids having nitrogen functional groups, exhibiting enhanced drug absorption and hence, improved drug efficiency of oral formulations such as oral tablets, enteral feeds or oral suspensions.

It would have been obvious to one skilled in the art at the time the invention was made to make complex with phosphate derivatives of electron transfer agents to bring about efficacious therapeutic effect in oral formulations with a reasonable expectation of success. Alternately, to use analgesic such as morphine in forming a reaction product with tocopherol phosphate derivative would have been obvious to one skilled in the art at the time the invention was made with a reasonable expectation of success because ('1720 teaches preparation of orally and buccaly administrable tablet and lozenges.

5. Claim 5 is rejected under 35 U.S.C. 103(a) as being unpatentable over Schor et al. (U.S. Patent No. 4,369,172, herein after ('172) in view of WO 02/40033 A1 ('033) and further in view of Fisher et al. (US 2004/0234602 A1).

The teachings of Schor et al. and WO 02/40033 A1 ('033) are discussed above.

Schor et al. and ('033) do not teach using enteric coatings in the oral formulations disclosed above.

However, Fischer et al. in US publication (U.S. 2004/0234602 A1) discloses a composition with enteric coating and a method for controlling the release of a therapeutically active substance from a pharmaceutical composition into an aqueous medium, wherein the pharmaceutical composition is a coated matrix composition in which the matrix comprises:

- a) Polymer or mixture of polymers,
 - b) An active substance and optionally,
 - c) One or more excipients
- (Page 1, paragraph 1)

- The polymers such as polyethylene oxide or eudragit L methyl ester as disclosed by Fischer et al. (on page 3, paragraph 41 and 43) are an example of enteric coatings. The active substance such as morphine, codeine and atropin can be used in the above composition (page 4, paragraph 51) in an oral formulation (page 3, paragraph 48). ('172) further teaches that in order to soften the "carrier system", a plasticizer can be selected from group of phosphate esters for e.g. α-tocopherylphosphate esters (page 8 paragraph 100).

Because Fischer et al. teaches that enteral coatings can be used to control release of drug and since it is well known in the art that enteral coatings are used to promote absorption of drugs in the intestine, it would have been obvious to one of ordinary skill in the art at the time the invention was made to use enteric coatings as taught by Fischer et al. in the teachings advanced by ('172) as modified by ('033). A skilled artisan

would be motivated to prepare enteric-coated oral formulations of alkaloids such as morphine or atropine complexed with phosphate derivatives of "electron transfer agents" or in other words phosphate derivatives of tocopherol with reasonable expectations of success because enteric coatings help in the absorption of the active substance in the intestine.

Response to Arguments

6. Applicant's arguments filed 06/06/07 have been fully considered but they are not persuasive.

Applicant argues that "acceptable carrier" as interpreted by the examiner is not a drug, food or cosmetics." Examiner notes that an "acceptable carrier" as interpreted by the examiner is not a drug, food or cosmetics, however examiner points to the teachings of ('033) which discloses that phosphate derivative of electron transfer agent may exist in the form of a phosphatidyl compound wherein the free phosphate oxygen forms a bond with an alkyl group or a complex with a complexing agent selected from amphoteric surfactant, cationic surfactant or aminoacids having nitrogen functional groups or proteins rich in these amino acids (see page 4, lines 8-11 and claim 4). Taking chemistry into consideration it can be said that since phosphate derivatives of tocopherol has been shown to form complex with aminoacids having **nitrogen functional groups**, the **nitrogen** is the critical element in forming a complex with tocopherol phosphate. In the absence of any definition provided by the applicants with

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regard to the limitation , “ reaction product” in the instant claims and by giving the claims the broadest reasonable interpretation, it is the position of the examiner, that it would have been obvious to one of ordinary skilled in the art at the time of the invention to use the phosphate derivatives of tocopherol ('033) in forming a complex with an alkaloid such as morphine which bears a functional nitrogen. Examiner cites (US Patent no. 6,479,540) as a reference to quote that pharmaceutically active amines, peptides and polypeptides form ion pair with tocopherol phosphate, retinoids, benzoquinone and esters of tocopherol phosphate and also pharmaceutically active compound cationic in nature forming complex with ion pair forming compound such as succinate or phosphate derivative of tocopherol (see claims and examples). Therefore, it would have been obvious to the one of ordinary skilled in the art at the time of the invention to formulate reaction product comprising morphine and tocopherol phosphate.

7. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

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the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

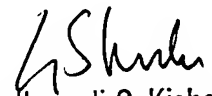
Any inquiry concerning this communication or earlier communications from the examiner should be directed to Snigdha Maewall whose telephone number is (571)-272-6197. The examiner can normally be reached on Monday-Friday from 8:30AM to 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward, can be reached on (571)-272-8373. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Snigdha Maewall

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